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	First Named Inventor	CALDWELL, LARRY
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	Group Art Unit	1618
	Examiner Name	OH, SIMON J.
	Title:	METHODS AND COMPOSITIONS FOR TREATING CARPAL TUNNEL SYNDROME

Dear Sir:

I, Bradley Galer, am an inventor of the subject matter claimed in the patent application identified above.

I hereby declare as follows:

1. I am the sole inventor on U.S. Application Serial No. 10/045,341 published as 20030124174 and U.S. Application Serial No. 11/336,001 published as 20060147510. Copies of these published applications are enclosed.

2. I have recently reviewed both of the above referenced applications and have found an error in their disclosures. Both U.S. Application Serial No. 10/045,341 and U.S. Application Serial No. 11/336,001 **erroneously** reference Carpal Tunnel Syndrome

as a type of "non-neuropathic pain." As is known in the art, Carpal Tunnel Syndrome is a type of neuropathic pain, and therefore is not a type of "non-neuropathic" pain.

3. Prior to filing of the '341 (the parent application of the '001 application), I instructed the prosecuting attorney to remove Carpel Tunnel Syndrome from the list of non-neuropathic pains referenced in the '341 and '001 applications.

4. At the time of signing the Oath and Declaration for the '341 application, I assumed that the prosecuting attorney had made my revisions and did not appreciate that my requested corrections to the previous drafts of the applications had not been made when I signed the Oath and Declaration.

5. Subsequent to the filing of the '341 application, I learned of the error described above. I have instructed the prosecuting attorney to make the appropriate corrections to the '341 and '001 disclosures.

6. Accordingly, once corrected, the '341 and '001 applications will not identify Carpal Tunnel Syndrome as a type of non-neuropathic pain.

I hereby declare that all statements made herein are of my own knowledge and are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued there from.

Respectfully submitted,

Date: 20 Nov 2006 By: _____

Bradley Galer

encs: 20030124174 and 20060147510

US 20030124174A1

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Galer (43) **Pub. Date: Jul. 3, 2003**

(54) **METHOD FOR TREATING NON-NEUROPATHIC PAIN**

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(51) **Int. Cl.**[7] **A61K 9/70**; A61K 31/24

(52) **U.S. Cl.** **424/449**; 514/536

(57) **ABSTRACT**

A method including topically administering an effective amount of local anesthetic to a patient is disclosed. The method is effective for inducing analgesia for treating non-neuropathic pain. Non-neuropathic pain suitable for treatment according to the invention includes pain associated with sports injuries; sprains; strains; soft-tissue injury; repetitive motion injury; carpal tunnel syndrome; injury to tendons, ligament, and muscles; conditions such as fibromyalgia, bursitis, castrochondritis, myofascial pain, and pain associated with arthritis, inflammation, contusions, post-surgical pain, and nociceptive pain. Preferably, the lidocaine is applied via a transdermal patch applied near the locus of pain.

METHOD FOR TREATING NON-NEUROPATHIC PAIN

FIELD OF INVENTION

[0001] The invention relates to methods of treating non-neuropathic pain. Specifically, the invention relates to methods of treating non-neuropathic pain by topically administering a local anesthetic, such as lidocaine, in an effective amount near the pain location. Most specifically, the invention relates to methods of treating non-neuropathic pain by administering a topical lidocaine patch to a patient, where the transdermal drug delivery results in no clinically meaningful serum drug levels nor produces anesthesia at the site of delivery, i.e. analgesia without anesthesia.

DESCRIPTION OF THE RELATED ART

[0002] Pain can be treated with either analgesics or anesthetics. A distinguishing feature of analgesics is that they reduce the perception of pain without causing numbness or complete loss of sensation associated with anesthetics.

[0003] Currently, prescription analgesics approved by the Food and Drug Administration (FDA) fall into only two classes of drugs: opioids and anti-inflammatories. Anesthetics fall into a different classification. Opioids work by mimicking the body's natural opioid-like substances, i.e. endorphins and enkaphalins, which are produced by the body to help alleviate pain. These substances, and the opioids, block pain by binding to the opioid receptors found throughout the central and peripheral nervous systems. Anti-inflammatories (including NSAIDs and COX-2 inhibitors) attempt to reduce inflammation produced by the prostaglandin chemical cascade resulting from bodily injury. The FDA recognizes only these two classes as "general analgesics."

[0004] Because of this classification, and the known drugs and their mechanisms of action, it is surprising to learn that a product, traditionally classified as an anesthetic, is useful as a general analgesic.

[0005] Pain, as discussed herein, falls into two broad categories: neuropathic pain and non-neuropathic pain. The methods associated with treating one type of pain are not necessarily effective at treating the other.

[0006] Neuropathic pain is a particular type of pain that has a complex and variable etiology, distinct from nociceptive or inflammatory pain. It is generally a chronic condition attributable to complete or partial transection of a nerve or trauma to a nerve plexus, whereas non-neuropathic pain, i.e. nociceptive or inflammatory pain, occurs in the setting of a normal undamaged nervous system. Neuropathic pain is characterized by hyperesthesia (enhanced sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to pain), allodynia (widespread tenderness, characterized by hypersensitivity to normoxious tactile stimuli), and/or spontaneous burning pain. In humans, neuropathic pain tends to be chronic and may be debilitating.

[0007] Non-neuropathic pain is just as complex and variable. Non-neuropathic pain includes common conditions such as arthritis pains, musculoskeletal pains, postoperative pains, and fibromyalgia. Most of these pains, such as arthritis pains, musculoskeletal pains, and postoperative pains, are thought to be caused by damage to soft tissue and bone, resulting in the natural inflammatory response in the face of a normally functioning nervous system. However, some non-neuropathic pains, are less well understood. Conditions, such as fibromyalgia, which lead to non-neuropathic pain despite the belief that the nervous system remains intact and undamaged, are not well understood themselves. Treating such conditions and the associated pain is often difficult due to this lack of understanding. It is an object of this invention to treat this and other non-neuropathic pain.

[0008] The invention revolves around the proposition that all pain, neuropathic or otherwise, is transmitted by specialized nerve fibers called "nociceptors." The normal undamaged nociceptor nerve is only physiologically active and gives a normal discharge (resulting in the perception of pain) when the area of skin it innervates is injured by burn, cut, or bruise. This discharge is a normal function of the nerve. Otherwise, the nerve is silent and no pain is perceived in this region of the body.

[0009] However, when the nociceptor peripheral nerve itself is damaged, i.e. neuropathic pain, abnormal sodium channels develop at the site of nerve damage, resulting in (1) ectopic abnormal discharges in the normally silent nociceptor nerve, which causes (2) the development of a pain signal in the nociceptor even though no skin damage has occurred, and hence (3) the perception of abnormal spontaneous neuropathic pain and its accompanying hyperalgesia, hyperasthesia, and allodynia in the skin region it innervates. This is not normal function or discharge. Moreover, because these abnormal sodium channels on the damaged nociceptor nerve have an extremely high affinity for sodium and sodium channel antagonist drugs, extremely low doses of sodium channel blocking drugs delivered by intravenous route, oral route, or topical route can bind to these abnormal sodium channels, reduce the frequency of these abnormal discharges, and thus result in the alleviation of neuropathic pain without the complete blockage of the nerve's transmission and without sensory loss or motor blockade.

[0010] However, heretofore, in non-neuropathic pain, because the nervous system, including the nociceptor nerve, is not damaged, it has been believed that these abnormal sodium channels do not develop and the pain is solely a result of the inflammatory process. Until now, treatment of normally firing, undamaged nerves by such low doses of sodium channel blocking drugs has not been used or even contemplated. Non-neuropathic pains have not been treated with very low dose sodium channel blocking agents, delivered by any route. Thus, non-neuropathic pains usually have been treated by NSAIDs and COX-2 drugs, that directly interfere with the inflammatory process. In treating such pains, anesthetics are usually injected directly into either the skin or the nerves in the region. The role of anesthetics in treating non-neuropathic pain results in complete sensory block (numbness) and/or complete motor blockade, thereby stopping the nerve's transmission completely, i.e. analgesia (pain relief) with anesthesia (sensory loss). Clinically, anesthesia is not usually the optimal pain treatment as it renders the patient with a numb body part and, at times, paralysis of the involved body region.

[0011] Lidocaine, a well-known topical anesthetic, has been used with success to treat pain associated with nerve injury (i.e. neuropathic pain). Because lidocaine is an anesthetic whose sole mechanism of action is peripheral sodium

channel antagonism, its use as an analgesic without anesthesia in treating non-neuropathic pain has, heretofore, gone unexplored. It is surprising and unexpected that such a powerful anesthetic useful in treating neuropathic pain is effective to produce analgesia when treating pain where nerve injury is known not to have occurred. Thus, pathophysiologic events associated with non-neuropathic pain must also, like neuropathic pain, involve the production of high affinity sodium channels in the painful regions' uninjured nociceptor nerves. It can, at this time, only be speculated that the normal release of inflammatory peptides, histamine, or other peptides and chemicals known to occur in non-neuropathic pain injury sites results in the development of high affinity sodium channels on the sites of adjacent nondamaged nociceptor nerves.

[0012] Because a great many injuries and pain, if not the majority of occurrences, are not neuropathic in origin, more and better methods of treating non-neuropathic pain are needed. Accordingly, the use of lidocaine as an analgesic without anesthesia in treating non-neuropathic pain can be a useful treatment where traditional analgesics and anesthetics might otherwise be used.

SUMMARY OF THE INVENTION

[0013] A method including topically administering an effective amount of a local anesthetic, such as but not limited to lidocaine, to a patient is disclosed. The method is effective for inducing analgesia without anesthesia for treating non-neuropathic pain. Non-neuropathic pain suitable for treatment according to the invention includes pain associated with sprains; strains; soft-tissue injury (bruises and the like); repetitive motion injury; carpal tunnel syndrome; injury to tendons, ligaments, and/or muscles; conditions such as fibromyalgia, bursitis, castrochondritis, myofascial pain, and pain associated with arthritis, inflammation, contusions, post-surgical pain, and nociceptive pain. Preferably, the local anesthetic, such as lidocaine, is applied via a transdermal patch applied on or adjacent to the locus of pain.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0014] The methods disclosed herein are merely illustrative in nature and are not intended to limit the scope of the invention as set forth in the claims below.

[0015] It has been discovered, that a topical local anesthetic drug, such as but not limited to lidocaine, has the ability to relieve pain associated with a wide variety of non-neuropathic pain associated with soft-tissue injury, arthritis, surgical procedures, and conditions such as fibromyalgia. This surprising and unexpected discovery has significance in the clinical setting and in the understanding of pathophysiological pain mechanisms. Other non-limiting examples of topical anesthetics which may be used include benzocaine, prilocaine, lidocaine, dubicaine, mepivacaine, bupivacaine, etc.

[0016] The finding strongly suggests that pain associated with these types of injuries and conditions is caused, at least to some degree, by the presence of dysfunctional sodium channels on non-damaged peripheral sensory nerves at the pain locus. Thus, a component of the pain perceived, which is associated with damage to non-nervous system peripheral tissues, is caused by abnormal ectopic nociceptive impulses that are generated by abnormal sodium channels.

[0017] It is known that damage to a peripheral sensory nerve produces abnormal ectopic nociceptive impulses and pain, i.e. neuropathic pain. Now, based on the findings above, it is hypothesized that injury to soft tissue results in the release of inflammatory and other chemicals and peptides that also cause the generation of abnormal sodium channels on local, undamaged sensory nerves. This then generates abnormal ectopic nociceptive impulses that result in the sensation/perception of pain at the site of soft-tissue injury.

[0018] Because of the generation of these normal nociceptive impulses produced in association with inflammation, the local presence of a sodium channel antagonist drug, such as lidocaine, binds to the abnormal sodium channels and reduces or abolishes the frequency of abnormal ectopic nociceptive impulses, and thereby results in alleviation of non-neuropathic pain. Importantly, and novel to this invention is the alleviation of non-neuropathic pain at the site of injury without the development of anesthesia or skin numbness.

[0019] Non-limiting examples of soft-tissue injuries include injury to the tendons, ligaments, muscles or bursa, and sprains and strains, etc. These, and other injuries, if occurring during a participation sport may be referred to as sports injuries. However, it makes no difference how the injury was received. The methods herein are effective in treating a broad range of such injuries. Other types of pain resulting from contusions, inflammation, bursitis, costrochondritis, and myofascial pains may also be treated. Other conditions, such as osteoarthritis, rheumatoid arthritis, fibromyalgia and carpal tunnel syndrome, that result in nociceptive pain can also be treated according to the invention.

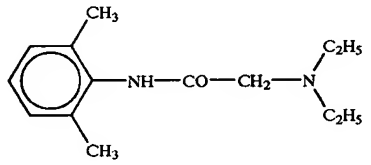
[0020] Fibromyalgia is a condition that is not easily diagnosed or treated. It is poorly understood with no agreed-upon underlying cause or pathophysiological mechanism. Many authorities believe it is caused by a disorder in the nervous system. Fibromyalgia is often associated with flu-like symptoms, including general body pain, coupled with points of sensitivity ("tender points") and pain at specific locations on the body. Despite the difficulty of treating this condition, treatment according to the method of the present invention can reduce the sensation/perception of pain associated with the condition without the development of anesthesia at the site of pain alleviation.

[0021] According to one embodiment, a transdermal patch containing 5% lidocaine is applied to the skin at or near the locus of pain. The patch may contain other pharmaceutically active ingredients, as is known in the art, or other ingredients to help transdermal migration of the active ingredient, stability of the patch, adhesion and other concerns. Currently preferred is the patch marketed as LIDODERM lidocaine patch, available from Endo Pharmaceuticals, Inc. Varying the size of the patch used varies the dosage. Often a patch is cut and only a portion is used. In some instances, the use of more than one patch may be advisable. Optimal pain relief often occurs when lidocaine patches are applied directly to the skin overlying the entire painful body region.

[0022] LIDODERM (lidocaine patch 5%) is comprised of an adhesive material containing 5% lidocaine, which is

applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm×14 cm.

[0023] Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol-:water partition ratio of 43 at pH 7.4, and has the following structure:



[0024] Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, D-sorbitol, tartaric acid, and urea.

[0025] Another embodiment includes administering a transdermal patch to the patient at the locus of pain where the patch contains approximately 5% lidocaine as the only active ingredient. The remainder of the patch consists of inactive pharmaceutically acceptable agents. Inactive agents do not, in and of themselves, relieve pain. Those skilled in the art will recognize the importance of these inactive agents which facilitate transfer of the lidocaine through the patch and skin, aid in forming the patch itself, or address other concerns and needs. Again, the dosage may be varied by varying the size of the patch.

[0026] Administration via transdermal patch is preferred because the application and release of lidocaine can be controlled through known techniques. Although the transdermal patch is preferred, topical application of a composition, including gels, salves, and ointments containing lidocaine will suffice. Topical application of such a composition, in effective amounts, will reduce the sensation/perception of pain in the local area. It should be noted, that when using the current LIDODERM patch delivery system, about 95% of the lidocaine remains unused. Accordingly, the amount of lidocaine or other anesthetic used will vary depending upon the efficiency of the delivery system. Directly applied gels, salves, ointments, etc. may require lesser amounts of the local anesthetic.

[0027] Importantly, because the pain associated with many of these injuries and conditions is nearly continuous and can extend over periods of time, the patient benefits greatly from being able to move about and continue with daily activities despite the pain associated with their conditions and injuries. Application of lidocaine as discussed above results in alleviation of pain (analgesia) without numbness or complete loss of sensation (anesthesia) or paralysis. This ability to alleviate pain without numbness or paralysis allows the patient, in many cases, to participate in many daily activities without being burdened by pain or numbness.

[0028] Further benefits from topical lidocaine administration are uniformity of treatment between patients since the drug is not subject to absorption through the digestive tract. This also reduces the likelihood of drug interactions and virtually eliminates the possibility of gastrointestinal distress associated with NSAIDs and with opioids. This treatment is particularly effective for strains, sprains, arthritis pains, and post-operative local surgical pain since the analgesic acts locally.

[0029] Further benefits include the lack of drug-drug interactions as no clinically meaningful plasma levels develops even with chronic usage.

[0030] Further benefits include the lack of the need to titrate the dose, commonly needed with other analgesics, such as NSAIDs, COX-2s, and opioids. Thus an effective dosage is delivered on the first dose. In addition, this may reduce the need for physician visits and phone calls that are associated with titration of medication dosages.

[0031] Case Studies

[0032] The following case studies are illustrative of the effectiveness of a lidocaine patch in treating various non-neuropathic pains. These are intended only as examples of treatment and are not meant to limit the scope of the claimed invention.

[0033] In case studies, many non-neuropathic pains were successfully treated with topical lidocaine patch. From these studies, it is known that topical lidocaine patch results in no clinically meaningful plasma lidocaine levels and no skin anesthesia nor motor block.

[0034] Lateral Epicondylitis; "Tennis Elbow":

[0035] A 39 year old male developed lateral epicondylitis ("tennis elbow") with localized pain and tenderness in the right elbow. The pain was constant and exacerbated by holding any object with his right hand and or any movement of the involved elbow. He placed one topical lidocaine patch (Lidoderm) directly on the skin overlying the painful elbow. Approximately several hours later he noted pain alleviation. He kept a lidocaine patch on his elbow for 3 consecutive days, replacing the patch with a new one every 24 hours, with excellent pain relief and no side effects. There was no appreciable numbness of the skin where the patch was placed. After 3 days of treatment, his pain was completely alleviated and he was able to lift objects and move his elbow joint without pain.

[0036] Arthritis:

[0037] Case 1

[0038] An 89 year old female was suffering with severe osteoarthritis pain of her knees. She was being treated with chronic corticosteroids (oral prednisone) for over 5 years. Initially, the steroids provided good pain relief but the pain gradually had returned over the immediate past year. Non-steroidal anti-inflammatory drugs were contraindicated due to her prior history of ulcers and the concomitant use of oral corticosteroids. She agreed to a trial of topical lidocaine patch, one patch placed over each knee for 12 hours application per day. After 1 week of treatment, she reported good pain relief in the arthritic knees and no side effects. She stated there was no "numbness" or change of sensation felt under the lidocaine patch.

[0039] Case 2

[0040] A 59 year old woman with rheumatoid arthritis affecting the elbow. She experiences intermittent severe pain that requires medication. She would rather not take anti-inflammatory medication due to side-effects. She was given lidocaine patch to apply to her painful elbow during these severe pain episodes. She reports a lot of pain relief with no side effects nor skin sensation changes when she applies topical lidocaine patch directly to the arthritic elbow for 24 hours.

[0041] Post-Operative Soft Tissue Pain:

[0042] A 46-year old male had undergone a surgical repair of a ruptured Achilles tendon. Following 6 weeks in a cast, he experienced moderate to moderately severe pain associated with movement of the surgically repaired Achilles tendon, especially associated with walking and later in the day after nonstrenuous daily activity. In the evening, he applied one patch directly to the skin overlying the Achilles tendon. Within 30-45 minutes he began to experience pain relief. While walking, he reported minimal pain and perceived improved mobility; this exact movement during similar times without the use of the lidocaine patch resulted in moderate to moderately-severe pain and a stiffer gait. Most noticeably, was that pain due to active walking was significantly reduced, but also low grade soreness due to a full day of walking was also significantly reduced. He kept the patch in place while sleeping resulting in minimal sleep interruption due to pain associated with movement during the night.

[0043] Ankle Sprain and Cramping Pain:

[0044] A 39 year old male suddenly experienced severe cramping pain in his left ankle one evening that prevented him for being able to fall asleep. The pain was so severe he was unable to put any weight on the ankle and had severe pain associated with flexion/extension of the ankle. He applied one topical lidocaine patch to the ankle and began to experience pain relief within 15 minutes. Within 1 hour, his pain was minimal and he was able to fall asleep. He awoke the next morning with no pain and was able to walk on the ankle with no pain. However, approximately 12 hours after patch application, the pain began to gradually return. Another patch was applied for 12 hours and the pain resolved again. When the second patch was removed 12 hours later, his pain was completely resolved and he was able to walk with no pain. No loss of sensation was noted on the skin where the patches were applied.

[0045] Poison Oak Pain/Itching:

[0046] A 39 year old female was suffering from pain and severe discomfort from itching on her arms due to poison oak. She applied lidocaine patches to the painful and itching skin region. Within 30 minutes she began to report relief of the pain and itching directly underlying the site of patch application. Within 1.5 hours she reported nearly complete pain and itching relief.

[0047] Those skilled in the art will appreciate other variations and improvements on the methods disclosed and claimed herein. All such obvious variants are considered within the spirit and scope of the claims below.

What is claimed is:

1. A method for treating non-neuropathic pain comprising topically administering a composition containing a local anesthetic to a patient near a pain locus in an amount sufficient to produce analgesia without causing anesthesia.

2. The method of claim 1 wherein said local anesthetic is lidocaine.

3. The method of claim 1 wherein said local anesthetic is applied from a transdermal patch.

4. The method of claim 3 wherein said patch comprises 1-10% local anesthetic.

5. The method of claim 3 wherein said patch comprises 11-10% lidocaine.

6. The method of claim 3 wherein said patch comprises 4-6% lidocaine.

7. The method of claim 2 wherein said local anesthetic is applied from a transdermal patch comprising 5% lidocaine.

8. The method of claim 1 wherein said non-neuropathic pain to be treated results from a soft-tissue injury.

9. The method of claim 8, wherein said soft-tissue injury is selected from the group consisting of pain associated with ligaments, tendons, muscles, bursa, sprains, strains, inflammations, contusions, arthritises, and post-surgical pains.

10. The method of claim 1 wherein said neuropathic pain is derived from one or more conditions selected from the group consisting of myofascial pains, fibromyalgia, bursitis, costrochondritis, repetitive motion injuries, carpal tunnel syndrome, and nociceptive pain.

11. A method for treating non-neuropathic pain comprising the step of:

topically administering a transdermal patch containing a pharmaceutical composition consisting of 5% lidocaine as an active ingredient, and the remainder consisting of inactive pharmaceutically acceptable materials.

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Galer (43) Pub. Date: Jul. 6, 2006

(54) METHOD FOR TREATING NON-NEUROPATHIC PAIN

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(22) Filed: **Jan. 20, 2006**

Related U.S. Application Data

(63) Continuation of application No. 10/045,341, filed on Oct. 25, 2001, now abandoned.

Publication Classification

(51) **Int. Cl.**
A61K 9/70 (2006.01)

(52) **U.S. Cl.** **424/449**

(57) **ABSTRACT**

A method including topically administering an effective amount of local anesthetic to a patient is disclosed. The method is effective for inducing analgesia for treating non-neuropathic pain. Non-neuropathic pain suitable for treatment according to the invention includes pain associated with sports injuries; sprains; strains; soft-tissue injury; repetitive motion injury; carpal tunnel syndrome; injury to tendons, ligament, and muscles; conditions such as fibromyalgia, bursitis, castrochondritis, myofascial pain, and pain associated with arthritis, inflammation, contusions, post-surgical pain, and nociceptive pain. Preferably, the lidocaine is applied via a transdermal patch applied near the locus of pain.

METHOD FOR TREATING NON-NEUROPATHIC PAIN

FIELD OF INVENTION

[0001] The invention relates to methods of treating non-neuropathic pain. Specifically, the invention relates to methods of treating non-neuropathic pain by topically administering a local anesthetic, such as lidocaine, in an effective amount near the pain location. Most specifically, the invention relates to methods of treating non-neuropathic pain by administering a topical lidocaine patch to a patient, where the transdermal drug delivery results in no clinically meaningful serum drug levels nor produces anesthesia at the site of delivery, i.e. analgesia without anesthesia.

DESCRIPTION OF THE RELATED ART

[0002] Pain can be treated with either analgesics or anesthetics. A distinguishing feature of analgesics is that they reduce the perception of pain without causing numbness or complete loss of sensation associated with anesthetics.

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[0004] Because of this classification, and the known drugs and their mechanisms of action, it is surprising to learn that a product, traditionally classified as an anesthetic, is useful as a general analgesic.

[0005] Pain, as discussed herein, falls into two broad categories: neuropathic pain and non-neuropathic pain. The methods associated with treating one type of pain are not necessarily effective at treating the other.

[0006] Neuropathic pain is a particular type of pain that has a complex and variable etiology, distinct from nociceptive or inflammatory pain. It is generally a chronic condition attributable to complete or partial transection of a nerve or trauma to a nerve plexus, whereas non-neuropathic pain, i.e. nociceptive or inflammatory pain, occurs in the setting of a normal undamaged nervous system. Neuropathic pain is characterized by hyperesthesia (enhanced sensitivity to a natural stimulus), hyperalgesia (abnormal sensitivity to pain), allodynia (widespread tenderness, characterized by hypersensitivity to nonnoxious tactile stimuli), and/or spontaneous burning pain. In humans, neuropathic pain tends to be chronic and may be debilitating.

[0007] Non-neuropathic pain is just as complex and variable. Non-neuropathic pain includes common conditions such as arthritis pains, musculoskeletal pains, postoperative pains, and fibromyalgia. Most of these pains, such as arthritis pains, musculoskeletal pains, and postoperative pains, are thought to be caused by damage to soft tissue and bone, resulting in the natural inflammatory response in the face of a normally functioning nervous system. However, some non-neuropathic pains, are less well understood. Conditions, such as fibromyalgia, which lead to non-neuropathic pain despite the belief that the nervous system remains intact and undamaged, are not well understood themselves. Treating such conditions and the associated pain is often difficult due to this lack of understanding. It is an object of this invention to treat this and other non-neuropathic pain.

[0008] The invention revolves around the proposition that all pain, neuropathic or otherwise, is transmitted by specialized nerve fibers called "nociceptors." The normal undamaged nociceptor nerve is only physiologically active and gives a normal discharge (resulting in the perception of pain) when the area of skin it innervates is injured by burn, cut, or bruise. This discharge is a normal function of the nerve. Otherwise, the nerve is silent and no pain is perceived in this region of the body.

[0009] However, when the nociceptor peripheral nerve itself is damaged, i.e. neuropathic pain, abnormal sodium channels develop at the site of nerve damage, resulting in (1) ectopic abnormal discharges in the normally silent nociceptor nerve, which causes (2) the development of a pain signal in the nociceptor even though no skin damage has occurred, and hence (3) the perception of abnormal spontaneous neuropathic pain and its accompanying hyperalgesia, hyperasthesia, and allodynia in the skin region it innervates. This is not normal function or discharge. Moreover, because these abnormal sodium channels on the damaged nociceptor nerve have an extremely high affinity for sodium and sodium channel antagonist drugs, extremely low doses of sodium channel blocking drugs delivered by intravenous route, oral route, or topical route can bind to these abnormal sodium channels, reduce the frequency of these abnormal discharges, and thus result in the alleviation of neuropathic pain without the complete blockage of the nerve's transmission and without sensory loss or motor blockade.

[0010] However, heretofore, in non-neuropathic pain, because the nervous system, including the nociceptor nerve, is not damaged, it has been believed that these abnormal sodium channels do not develop and the pain is solely a result of the inflammatory process. Until now, treatment of normally firing, undamaged nerves by such low doses of sodium channel blocking drugs has not been used or even contemplated. Non-neuropathic pains have not been treated with very low dose sodium channel blocking agents, delivered by any route. Thus, non-neuropathic pains usually have been treated by NSAIDs and COX-2 drugs, that directly interfere with the inflammatory process. In treating such pains, anesthetics are usually injected directly into either the skin or the nerves in the region. The role of anesthetics in treating non-neuropathic pain results in complete sensory block (numbness) and/or complete motor blockade, thereby stopping the nerve's transmission completely, i.e. analgesia (pain relief) with anesthesia (sensory loss). Clinically, anesthesia is not usually the optimal pain treatment as it renders the patient with a numb body part and, at times, paralysis of the involved body region.

[0011] Lidocaine, a well-known topical anesthetic, has been used with success to treat pain associated with nerve injury (i.e. neuropathic pain). Because lidocaine is an anesthetic whose sole mechanism of action is peripheral sodium

channel antagonism, its use as an analgesic without anesthesia in treating non-neuropathic pain has, heretofore, gone unexplored. It is surprising and unexpected that such a powerful anesthetic useful in treating neuropathic pain is effective to produce analgesia when treating pain where nerve injury is known not to have occurred. Thus, pathophysiologic events associated with non-neuropathic pain must also, like neuropathic pain, involve the production of high affinity sodium channels in the painful regions' uninjured nociceptor nerves. It can, at this time, only be speculated that the normal release of inflammatory peptides, histamine, or other peptides and chemicals known to occur in non-neuropathic pain injury sites results in the development of high affinity sodium channels on the sites of adjacent nondamaged nociceptor nerves.

[0012] Because a great many injuries and pain, if not the majority of occurrences, are not neuropathic in origin, more and better methods of treating non-neuropathic pain are needed. Accordingly, the use of lidocaine as an analgesic without anesthesia in treating non-neuropathic pain can be a useful treatment where traditional analgesics and anesthetics might otherwise be used.

SUMMARY OF THE INVENTION

[0013] A method including topically administering an effective amount of a local anesthetic, such as but not limited to lidocaine, to a patient is disclosed. The method is effective for inducing analgesia without anesthesia for treating non-neuropathic pain. Non-neuropathic pain suitable for treatment according to the invention includes pain associated with sprains; strains; soft-tissue injury (bruises and the like); repetitive motion injury; carpal tunnel syndrome; injury to tendons, ligaments, and/or muscles; conditions such as fibromyalgia, bursitis, castrochondritis, myofascial pain, and pain associated with arthritis, inflammation, contusions, post-surgical pain, and nociceptive pain. Preferably, the local anesthetic, such as lidocaine, is applied via a transdermal patch applied on or adjacent to the locus of pain.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0014] The methods disclosed herein are merely illustrative in nature and are not intended to limit the scope of the invention as set forth in the claims below.

[0015] It has been discovered, that a topical local anesthetic drug, such as but not limited to lidocaine, has the ability to relieve pain associated with a wide variety of non-neuropathic pain associated with soft-tissue injury, arthritis, surgical procedures, and conditions such as fibromyalgia. This surprising and unexpected discovery has significance in the clinical setting and in the understanding of pathophysiological pain mechanisms. Other non-limiting examples of topical anesthetics which may be used include benzocaine, prilocalne, lidocaine, dubicaine, mepivacaine, bupivacaine, etc.

[0016] The finding strongly suggests that pain associated with these types of injuries and conditions is caused, at least to some degree, by the presence of dysfunctional sodium channels on non-damaged peripheral sensory nerves at the pain locus. Thus, a component of the pain perceived, which is associated with damage to non-nervous system peripheral tissues, is caused by abnormal ectopic nociceptive impulses that are generated by abnormal sodium channels.

[0017] It is known that damage to a peripheral sensory nerve produces abnormal ectopic nociceptive impulses and pain, i.e. neuropathic pain. Now, based on the findings above, it is hypothesized that injury to soft tissue results in the release of inflammatory and other chemicals and peptides that also cause the generation of abnormal sodium channels on local, undamaged sensory nerves. This then generates abnormal ectopic nociceptive impulses that result in the sensation/perception of pain at the site of soft-tissue injury.

[0018] Because of the generation of these normal nociceptive impulses produced in association with inflammation, the local presence of a sodium channel antagonist drug, such as lidocaine, binds to the abnormal sodium channels and reduces or abolishes the frequency of abnormal ectopic nociceptive impulses, and thereby results in alleviation of non-neuropathic pain. Importantly, and novel to this invention is the alleviation of non-neuropathic pain at the site of injury without the development of anesthesia or skin numbness.

[0019] Non-limiting examples of soft-tissue injuries include injury to the tendons, ligaments, muscles or bursa, and sprains and strains, etc. These, and other injuries, if occurring during a participation sport may be referred to as sports injuries. However, it makes no difference how the injury was received. The methods herein are effective in treating a broad range of such injuries. Other types of pain resulting from contusions, inflammation, bursitis, costrochondritis, and myofascial pains may also be treated. Other conditions, such as osteoarthritis, rheumatoid arthritis, fibromyalgia and carpal tunnel syndrome, that result in nociceptive pain can also be treated according to the invention.

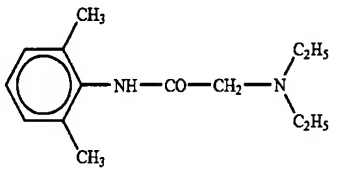
[0020] Fibromyalgia is a condition that is not easily diagnosed or treated. It is poorly understood with no agreed-upon underlying cause or pathophysiological mechanism. Many authorities believe it is caused by a disorder in the nervous system. Fibromyalgia is often associated with flu-like symptoms, including general body pain, coupled with points of sensitivity ("tender points") and pain at specific locations on the body. Despite the difficulty of treating this condition, treatment according to the method of the present invention can reduce the sensation/perception of pain associated with the condition without the development of anesthesia at the site of pain alleviation.

[0021] According to one embodiment, a transdermal patch containing 5% lidocaine is applied to the skin at or near the locus of pain. The patch may contain other pharmaceutically active ingredients, as is known in the art, or other ingredients to help transdermal migration of the active ingredient, stability of the patch, adhesion and other concerns. Currently preferred is the patch marketed as LIDODERM lidocaine patch, available from Endo Pharmaceuticals, Inc. Varying the size of the patch used varies the dosage. Often a patch is cut and only a portion is used. In some instances, the use of more than one patch may be advisable. Optimal pain relief often occurs when lidocaine patches are applied directly to the skin overlying the entire painful body region.

[0022] LIDODERM (lidocaine patch 5%) is comprised of an adhesive material containing 5% lidocaine, which is

applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm×14 cm.

[0023] Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol-:water partition ratio of 43 at pH 7.4, and has the following structure:



[0024] Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacryslate, D-sorbitol, tartaric acid, and urea.

[0025] Another embodiment includes administering a transdermal patch to the patient at the locus of pain where the patch contains approximately 5% lidocaine as the only active ingredient. The remainder of the patch consists of inactive pharmaceutically acceptable agents. Inactive agents do not, in and of themselves, relieve pain. Those skilled in the art will recognize the importance of these inactive agents which facilitate transfer of the lidocaine through the patch and skin, aid in forming the patch itself, or address other concerns and needs. Again, the dosage may be varied by varying the size of the patch.

[0026] Administration via transdermal patch is preferred because the application and release of lidocaine can be controlled through known techniques. Although the transdermal patch is preferred, topical application of a composition, including gels, salves, and ointments containing lidocaine will suffice. Topical application of such a composition, in effective amounts, will reduce the sensation/perception of pain in the local area. It should be noted, that when using the current LIDODERM patch delivery system, about 95% of the lidocaine remains unused. Accordingly, the amount of lidocaine or other anesthetic used will vary depending upon the efficiency of the delivery system. Directly applied gels, salves, ointments, etc. may require lesser amounts of the local anesthetic.

[0027] Importantly, because the pain associated with many of these injuries and conditions is nearly continuous and can extend over periods of time, the patient benefits greatly from being able to move about and continue with daily activities despite the pain associated with their conditions and injuries. Application of lidocaine as discussed above results in alleviation of pain (analgesia) without numbness or complete loss of sensation (anesthesia) or paralysis. This ability to alleviate pain without numbness or paralysis allows the patient, in many cases, to participate in many daily activities without being burdened by pain or numbness.

[0028] Further benefits from topical lidocaine administration are uniformity of treatment between patients since the drug is not subject to absorption through the digestive tract. This also reduces the likelihood of drug interactions and virtually eliminates the possibility of gastro-intestinal distress associated with NSAIDs and with opioids. This treatment is particularly effective for strains, sprains, arthritis pains, and post-operative local surgical pain since the analgesic acts locally.

[0029] Further benefits include the lack of drug-drug interactions as no clinically meaningful plasma levels develops even with chronic usage.

[0030] Further benefits include the lack of the need to titrate the dose, commonly needed with other analgesics, such as NSAIDs, COX-2s, and opioids. Thus an effective dosage is delivered on the first dose. In addition, this may reduce the need for physician visits and phone calls that are associated with titration of medication dosages.

Case Studies

[0031] The following case studies are illustrative of the effectiveness of a lidocaine patch in treating various non-neuropathic pains. These are intended only as examples of treatment and are not meant to limit the scope of the claimed invention.

[0032] In case studies, many non-neuropathic pains were successfully treated with topical lidocaine patch. From these studies, it is known that topical lidocaine patch results in no clinically meaningful plasma lidocaine levels and no skin anesthesia nor motor block.

[0033] Lateral Epicondylitis; "Tennis Elbow":

[0034] A 39 year old male developed lateral epicondylitis ("tennis elbow") with localized pain and tenderness in the right elbow. The pain was constant and exacerbated by holding any object with his right hand and or any movement of the involved elbow. He placed one topical lidocaine patch (Lidoderm) directly on the skin overlying the painful elbow. Approximately several hours later he noted pain alleviation. He kept a lidocaine patch on his elbow for 3 consecutive days, replacing the patch with a new one every 24 hours, with excellent pain relief and no side effects. There was no appreciable numbness of the skin where the patch was placed. After 3 days of treatment, his pain was completely alleviated and he was able to lift objects and move his elbow joint without pain.

[0035] Arthritis:

[0036] Case 1

[0037] An 89 year old female was suffering with severe osteoarthritis pain of her knees. She was being treated with chronic corticosteroids (oral prednisone) for over 5 years. Initially, the steroids provided good pain relief but the pain gradually had returned over the immediate past year. Non-steroidal anti-inflammatory drugs were contraindicated due to her prior history of ulcers and the concomitant use of oral corticosteroids. She agreed to a trial of topical lidocaine patch, one patch placed over each knee for 12 hours application per day. After 1 week of treatment, she reported good pain relief in the arthritic knees and no side effects. She stated there was no "numbness" or change of sensation felt under the lidocaine patch.

[0038] Case 2

[0039] A 59 year old woman with rheumatoid arthritis affecting the elbow. She experiences intermittent severe pain that requires medication. She would rather not take anti-inflammatory medication due to side-effects. She was given lidocaine patch to apply to her painful elbow during these severe pain episodes. She reports a lot of pain relief with no side effects nor skin sensation changes when she applies topical lidocaine patch directly to the arthritic elbow for 24 hours.

[0040] Post-Operative Soft Tissue Pain:

[0041] A 46-year old male had undergone a surgical repair of a ruptured Achilles tendon. Following 6 weeks in a cast, he experienced moderate to moderately severe pain associated with movement of the surgically repaired Achilles tendon, especially associated with walking and later in the day after nonstrenuous daily activity. In the evening, he applied one patch directly to the skin overlying the Achilles tendon. Within 30-45 minutes he began to experience pain relief. While walking, he reported minimal pain and perceived improved mobility; this exact movement during similar times without the use of the lidocaine patch resulted in moderate to moderately-severe pain and a stiffer gait. Most noticeably, was that pain due to active walking was significantly reduced, but also low grade soreness due to a full day of walking was also significantly reduced. He kept the patch in place while sleeping resulting in minimal sleep interruption due to pain associated with movement during the night.

[0042] Ankle Sprain and Cramping Pain:

[0043] A 39 year old male suddenly experienced severe cramping pain in his left ankle one evening that prevented him for being able to fall asleep. The pain was so severe he was unable to put any weight on the ankle and had severe pain associated with flexion/extension of the ankle. He applied one topical lidocaine patch to the ankle and began to experience pain relief within 15 minutes. Within 1 hour, his pain was minimal and he was able to fall asleep. He awoke the next morning with no pain and was able to walk on the ankle with no pain. However, approximately 12 hours after patch application, the pain began to gradually return. Another patch was applied for 12 hours and the pain resolved again. When the second patch was removed 12 hours later, his pain was completely resolved and he was able to walk with no pain. No loss of sensation was noted on the skin where the patches were applied.

[0044] Poison Oak Pain/Itching:

[0045] A 39 year old female was suffering from pain and severe discomfort from itching on her arms due to poison oak. She applied lidocaine patches to the painful and itching skin region. Within 30 minutes she began to report relief of the pain and itching directly underlying the site of patch application. Within 1.5 hours she reported nearly complete pain and itching relief.

[0046] Those skilled in the art will appreciate other variations and improvements on the methods disclosed and claimed herein. All such obvious variants are considered within the spirit and scope of the claims below.

1.-11. (canceled)

12. A method for treating non-neuropathic pain comprising topically administering a composition containing 4-6% lidocaine to non-damaged peripheral sensory nerves of a human patient near a pain locus in an amount sufficient to produce analgesia without causing anesthesia wherein said composition is incorporated into a topical patch for application to skin for a period of at least 12 hours.

13. The method of claim 12 wherein said non-neuropathic pain to be treated results from a soft-tissue injury.

14. The method of claim 13, wherein said soft-tissue injury is selected from the group consisting of pain associated with ligaments, tendon, muscles, bursa, sprains, strains, inflammations, contusions, arthritises, and post-surgical pains.

15. The method of claim 12 wherein said non-neuropathic pain is derived from one or more conditions selected from the group consisting of myofascial pains, fibromyalgia, bursitis, costrochondritis, repetitive motion injuries, carpal tunnel syndrome, and nociceptive pain.

16. A method for treating non-neuropathic pain comprising the step of:

topically administering to non-damaged peripheral sensory nerves at a pain locus, for a period of at least 12 hours, a patch containing a pharmaceutical composition consisting of 4-6% lidocaine as the only active ingredient, the remainder consisting of inactive pharmaceutically acceptable materials.

17. A method for treating non-neuropathic pain comprising topically administering a composition containing 4-6% lidocaine as the only active ingredient to non-damaged peripheral sensory nerves of a patient near a pain locus in an amount sufficient to produce analgesia.

18. The method of claim 17 wherein said non-neuropathic pain is derived from one or more conditions selected from the group consisting of myofascial pains, fibromyalgia, bursitis, costrochondritis, repetitive motion injuries, carpal tunnel syndrome, and nociceptive pain.

19. The method of claim 17 wherein said non-neuropathic pain to be treated results from a soft-tissue injury.

20. The method of claim 19, wherein said soft-tissue injury is selected from the group consisting of pain associated with ligaments, tendons, muscles, bursa, sprains, strains, inflammations, contusions, arthritises, and post-surgical pains.

21. The method of claim 16 wherein said patch contains 5% lidocaine.

22. The method of claim 12 wherein said patch contains 5% lidocaine, and said administration is for a period of at least 24 hours.

23. The method of claim 12 wherein said non-neuropathic pain to be treated results from arthritis.

24. A method for treating non-neuropathic pain comprising topically administering a composition containing lidocaine as the only active ingredient to non-damaged peripheral sensory nerves in a patient near a pain locus in an amount sufficient to produce analgesia.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Larry Caldwell, et al.	Art Unit: 1618
Serial No. 10/029,408	Examiner: Oh, Simon J.
Filed: December 26, 2001	Atty. Ref. CALD005
For: *Methods and Compositions for Treating Carpal Tunnel Syndrome*	

DECLARATION UNDER 37 C.F.R. 1.132

The Commissioner for Patents
Washington D.C. 20231

Dear Sir,

I, Bradley Galer, am a co-inventor of the subject matter claimed in the patent application identified above. A copy of my C.V. which demonstrates that I am qualified to speak on the level of one of skill in the art is already of record in the present application.

I hereby declare as follows:

1. I have read the Office Action dated June 29, 2006 for the above referenced application, as well as the references cited therein to support the rejections made by the Examiner.

2. US Patent No. 6,399,093 (the '093 patent) describes a method and composition to treat musculoskeletal compositions.

(a) The '093 patent does not teach or suggest the application of an NSAID formulation to an area about the carpal tunnel/median nerve.

(b) The only mention of carpal tunnel syndrome (CTS) in the '093 patent is a notation in the background section that describes that occupational injury may result in musculoskeletal injuries and notes CTS as an occupational hazard (abstract, col. 1, lines 27-43).

(c) The'093 patent does not specifically describe the treatment of carpal tunnel syndrome.

3. US Patent No. 5,980,921 (the '921 patent) describes topical compositions for regulating the oily/shiny appearance of skin.

(a) The '921 patent does not teach or suggest the application of an NSAID formulation to an area about the carpal tunnel/median nerve.

(b) The '921 patent does not describe the treatment of carpal tunnel syndrome.

4. US Patent No. 5,989,559 (the '599 patent) describes a banana peel extract composition and method of extraction. The '599 patent does not teach or suggest the application of an NSAID formulation to an area about the carpal tunnel/median nerve.

5. I am aware of no report of using a topical NSAID to treat carpal tunnel prior to the priority date of my application.

6. Prior to the work described in the subject application, one of skill in the art could not have had a reasonable expectation of success in a method of topically applying an

NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure. This lack of reasonable expectation of success in the claimed methods is based on the following premises:

(a) It is well known in the art that just because an active agent is administered orally to treat a medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition.

(i) In support of this statement, please see Exhibit A to this declaration which provides a copy of the abstract of Moore et al., Br. J. Clin. Pharmacol. (1994) 37:227-30. This abstract reports that topical application of morphine had no significant effect when compared with placebo for the treatment of pain. Since oral administration of morphine is known to be effective in treating post-operative pain, including that associated with bilateral molar surgery, this abstract demonstrates that just because an active agent is administered orally to treat a given medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition.

(ii) In further support of this statement, please see Exhibit A to this declaration which also provides a copy of the abstract of Lynch et al., Anesthesiology (2005) 103:140-6. This abstract reports that use of a topical 2% amitriptyline formulation in treating patients with neuropathic pain had no significant effect when compared with placebo. Since oral administration of amitriptyline is known to be effective in the treatment of neuropathic pain, this abstract also demonstrates that just because an active agent is administered orally to treat a given medical condition does not mean that it can be effective when administered topically to treat the same or different medical condition.

(b) It is well known in the art that just because an active agent is administered topically to treat one condition does not mean that it can be effective when topically administered to treat other conditions. In support of this statement, please see Exhibit B which is a reprint of news article reporting that topical application of a lidocaine formulation was ineffective in treating pain associated with post-surgical or post-traumatic sutured wound. This result is in contrast with the FDA approved use of a topical application of lidocaine for the treatment of Post Herpetic Neuralgia. See Exhibit C which provides the product label for LIDODERM®. As such, just because an active agent is administered topically to treat one condition, such as lidocaine for PHN, does not meant that the same agent can be effective when topically administered to treat other conditions, as evidenced by the failure of a topical lidocaine formulation to effectively treat pain associated with post-surgical or post-traumatic sutured wound.

(c) Because of the location of the target nerves which are responsible for carpal tunnel syndrome, it was not at all certain that the claimed methods would work prior to the actual reduction to practice reported in the application.

In the subject methods, the active agent must cross a barrier to reach the target site to be effective. Barriers are present in the area of the carpal tunnel/median nerve. The carpal tunnel is the interior of the wrist through which the medial nerve, tendons and blood vessels pass. Three sides of the carpal tunnel are bone and the other side is a thickened sheath, the flexor retinaculum, which is made of ligament material. Accordingly, for the subject methods to work, the target agent must cross this bone/ sheath barrier.

Furthermore, the active agent must penetrate deeply in order to reach a target site because carpal tunnel syndrome originates deep within the nerves of the wrist. Prior to my work in reducing the invention to practice, it was not at all certain that a sufficient amount of a given active agent would penetrate deeply enough to reach the target site.

Accordingly, in view of the above, based on the cited prior art teachings but without actual reduction to practice evidence, one of skill in the art would not have had a reasonable expectation of success in the claimed methods of topically applying an NSAID formulation to an area about the carpal tunnel/median nerve to treat carpal tunnel syndrome/median nerve pressure would be successful.

I hereby declare that all statements made herein of my own knowledge and are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued therefrom.

Respectfully submitted,

Date: 20 Nov 2006

Bradley Galer

enc:

- Exhibit A-Abstracts of Lynch et al. and Moore et al.
- Exhibit B - Reprint of " Epicept Announces Results Of European Phase III Trial For Lidopain® SP"
- Exhibit C-Lidoderm® product label

Exhibit A

1: Br J Clin Pharmacol. 1994 Mar;37(3):227-30. Links

The efficacy of locally applied morphine in post-operative pain after bilateral third molar surgery.

- Moore UJ,
- Seymour RA,
- Gilroy J,
- Rawlins MD.

Dental School, Newcastle upon Tyne.

1. Recent evidence has hinted at a peripheral site of action of morphine analgesic efficacy. 2. Previous studies by the same authors have developed a model for testing local analgesic efficacy by placing drugs into tooth sockets after third molar surgery. 3. The present studies test the hypothesis of local morphine activity at two dosage concentrations, 100 ng ml-1 and 100 micrograms ml-1 after third molar surgery. 4. No significant analgesic efficacy was found at either dose when compared with placebo.

PMID: 8198929 [PubMed - indexed for MEDLINE]

1: Anesthesiology. 2005 Jul;103(1):140-6. Wolters Kluwer | Lippincott Williams & Wilkins Links

Topical 2% amitriptyline and 1% ketamine in neuropathic pain syndromes: a randomized, double-blind, placebo-controlled trial.

- Lynch ME,
- Clark AJ,
- Sawynok J,
- Sullivan MJ.

Pain Management Unit, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada. mary.lynch@dal.ca

BACKGROUND: A double-blind, randomized, placebo-controlled 3-week study evaluated the efficacy of topical 2% amitriptyline, 1% ketamine, and a combination of both in treating patients with neuropathic pain. METHODS: Ninety-two patients with diabetic neuropathy, postherpetic neuralgia, or postsurgical/posttraumatic neuropathic pain with allodynia, hyperalgesia, or pinprick hypesthesia were randomly assigned to receive one of four creams (placebo, 2% amitriptyline, 1% ketamine, or 2% amitriptyline-1% ketamine combined). The primary outcome measure was change in average daily pain

intensity (baseline week vs. final week) using an 11-point numerical pain rating scale. Secondary outcomes included the McGill Pain Questionnaire, measures of allodynia and hyperalgesia, and patient satisfaction. RESULTS: A reduction in pain scores of 1.1-1.5 units was observed in all groups, and there was no difference between groups. Blood concentrations revealed no significant systemic absorption. Minimal side effects were encountered. CONCLUSION: This randomized, placebo-controlled trial examining topical 2% amitriptyline, 1% ketamine, and a combination in the treatment of neuropathic pain revealed no difference between groups. Optimization of doses may be required, because another study has revealed that higher concentrations of these agents combined do produce significant analgesia.

PMID: 15983466 [PubMed - indexed for MEDLINE]

Exhibit B

9.05.06 – Press Release

Epicept Announces Results Of European Phase III Trial For Lidopain® SP

Englewood Cliffs, NJ, September 5, 2006 - EpiCept Corporation (Nasdaq and OMX Stockholm: EPCT) announced today that LidoPAIN® SP, a sterile prescription analgesic patch designed to provide sustained **topical delivery of lidocaine to a post-surgical or post-traumatic sutured wound, did not meet its co-primary endpoints in a Phase III** clinical trial in Europe. (emphasis added)

The Phase III clinical trial was a randomized, double-blind, placebo-controlled trial of 440 patients who underwent hernia repair surgery. The trial results indicate that LidoPAIN SP did not achieve a statistically significant effect relative to placebo with respect to the primary endpoint of self-assessed pain intensity between 4 and 24 hours. In addition, a statistically significant effect was not achieved in the trial's co-primary endpoint of patient use of "rescue" medications, i.e. systemically-delivered analgesics used to alleviate pain.

The Company's initial analysis of the trial data indicates that the total amount of pain from 4-24 hours as measured by the area under the curve (AUC) had a p value of approximately 0.4; the co-primary endpoint of rescue medication use from hours 4-24 had a p value of approximately 0.09. Both treatment groups showed an analgesic effect with the greater analgesic response in the active group. The product was well tolerated in all treatment groups.

Exhibit C

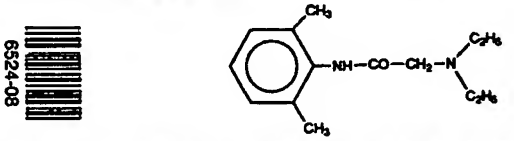
ENDO PHARMACEUTICALS

LIDODERM®
(Lidocaine Patch 5%)

R_x only

DESCRIPTION
LIDODERM (lidocaine patch 5%) is comprised of an adhesive material containing 5% lidocaine, which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner. The release liner is removed prior to application to the skin. The size of the patch is 10 cm x 14 cm.

Lidocaine is chemically designated as acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl), has an octanol:water partition ratio of 43 at pH 7.4, and has the following structure:



Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base. It also contains the following inactive ingredients: dihydroxyaluminum aminoacetate, disodium edetate, gelatin, glycerin, kaolin, methylparaben, polyacrylic acid, polyvinyl alcohol, propylene glycol, propylparaben, sodium carboxymethylcellulose, sodium polyacrylate, D-sorbitol, tartaric acid, and urea.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses.

The penetration of lidocaine into intact skin after application of LIDODERM is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

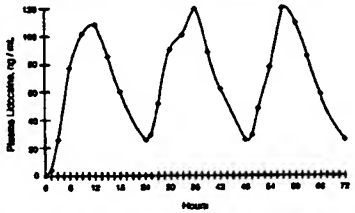
Pharmacokinetics
Absorption: The amount of lidocaine systemically absorbed from LIDODERM is directly related to both the duration of application and the surface area over which it is applied. In a pharmacokinetic study, three LIDODERM patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hours. Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches. The results are summarized in Table 1.

Table 1
Absorption of lidocaine from LIDODERM
Normal volunteers (n = 15, 12-hour wearing time)

LIDODERM Patch	Application Site	Area (cm^2)	Dose Absorbed (mg)	C_{max} (µg/mL)	T_{max} (hr)
3 patches (2100 mg)	Back	420	64 ± 32	0.13 ± 0.06	11 hr

When LIDODERM is used according to the recommended dosing instructions, only 3 ± 2% of the dose applied is expected to be absorbed. At least 95% (665 mg) of lidocaine will remain in a used patch. Mean peak blood concentration of lidocaine is about 0.13 µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias). Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose), once per day for three days, indicated that the lidocaine concentration does not increase with daily use. The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1.

Figure 1
Mean lidocaine blood concentrations after three consecutive daily applications of three LIDODERM patches simultaneously for 12 hours per day in healthy volunteers (n = 15).



Distribution: When lidocaine is administered intravenously to healthy volunteers, the volume of distribution is 0.7 to 2.7 L/kg (mean 1.5 ± 0.6 SD, n = 15). At concentrations produced by application of LIDODERM, lidocaine is approximately 70% bound to plasma proteins, primarily alpha-1-acid glycoprotein. At much higher plasma concentrations (1 to 4 µg/mL of free base), the plasma protein binding of lidocaine is concentration dependent. Lidocaine crosses the placental and blood brain barriers, presumably by passive diffusion.

Metabolism: It is not known if lidocaine is metabolized in the skin. Lidocaine is metabolized rapidly by the liver to a number of metabolites, including monoethylglycinexylidide (MEGX) and glycinexylidide (GX), both of which have pharmacologic activity similar to, but less potent than that of lidocaine. A minor metabolite, 2,6-xylidine, has unknown pharmacologic activity but is carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM (lidocaine patch 5%). Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively.

Excretion: Lidocaine and its metabolites are excreted by the kidneys. Less than 10% of lidocaine is excreted unchanged. The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD, n = 15). The systemic clearance is 0.33 to 0.90 L/min (mean 0.64 ± 0.18 SD, n = 15).

CLINICAL STUDIES
Single-dose treatment with LIDODERM was compared to treatment with vehicle patch (without lidocaine), and to no treatment (observation only) in a double-blind, crossover clinical trial with 35 post-herpetic neuralgia patients. Pain intensity and pain relief scores were evaluated periodically for 12 hours. LIDODERM performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours.

Multiple-dose, two-week treatment with LIDODERM was compared to vehicle patch (without lidocaine) in a double-blind, crossover clinical trial of withdrawal-type design conducted in 32 patients, who were considered as responders to the open-label use of LIDODERM prior to the study. The constant type of pain was evaluated but not the pain induced by sensory stimuli (dysesthesia). Statistically significant differences favoring LIDODERM were observed in terms of time to exit from the trial (14 versus 3.8 days at p-value <0.001), daily average pain relief, and patient's preference of treatment. About half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia. The extent of use of concomitant medication was similar in the two treatment groups.

INDICATION AND USAGE
LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin.

CONTRAINDICATIONS
LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

WARNINGS
Accidental Exposure to Children
Even a *used* LIDODERM patch contains a large amount of lidocaine (at least 665 mg). The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch, although the risk with this formulation has not been evaluated. It is important for patients to store and dispose of LIDODERM out of the reach of children and pets.

Excessive Dosing
Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations, leading to serious adverse effects (see ADVERSE REACTIONS, Systemic Reactions). Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/mL. The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination. Longer duration of application, application of more than the recommended number of patches, smaller patients, or impaired elimination may all contribute to increasing the blood concentration of lidocaine. With recommended dosing of LIDODERM, the average peak blood concentration is about 0.13 µg/mL, but concentrations higher than 0.25 µg/mL have been observed in some individuals.

PRECAUTIONS
General
Hepatic Disease: Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine, because of their inability to metabolize lidocaine normally.

Allergic Reactions: Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine. However, LIDODERM should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Non-Intact Skin: Application to broken or inflamed skin, although not tested, may result in higher blood concentrations of lidocaine from increased absorption. LIDODERM is only recommended for use on intact skin.

Eye Exposure: The contact of LIDODERM with eyes, although not studied, should be avoided based on the findings of severe eye irritation with the use of similar products in animals. If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns.

Drug Interactions
Antiarrhythmic Drugs: LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.

Local Anesthetics: When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: A minor metabolite, 2,6-xylidine, has been found to be carcinogenic in rats. The blood concentration of this metabolite is negligible following application of LIDODERM.

Mutagenesis: Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleous test.

Impairment of Fertility: The effect of LIDODERM on fertility has not been studied.

Pregnancy
Teratogenic Effects: Pregnancy Category B. LIDODERM (lidocaine patch 5%) has not been studied in pregnancy. Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LIDODERM should be used during pregnancy only if clearly needed.

Labor and Delivery
LIDODERM has not been studied in labor and delivery. Lidocaine is not contraindicated in labor and delivery. Should LIDODERM be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered.

Nursing Mothers
LIDODERM has not been studied in nursing mothers. Lidocaine is excreted in human milk, and the milk:plasma ratio of lidocaine is 0.4. Caution should be exercised when LIDODERM is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Application Site Reactions

During or immediately after treatment with LIDODERM (lidocaine patch 5%), the skin at the site of application may develop erythema, edema, bruising, papules, vesicles, discoloration, depigmentation, burning sensation, pruritus, dermatitis, petechia, blisters, excitation, or may be the locus of abnormal sensation. These reactions are generally mild and transient, resolving spontaneously within a few minutes to hours.

Allergic Reactions

Allergic and anaphylactoid reactions associated with lidocaine, although rare, can occur. They are characterized by urticaria, angioedema, bronchospasm, laryngospasm, dermatitis, pruritus, dyspnea, and shock. If they occur, they should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Events Observed During Postmarketing Surveillance of LIDODERM

Due to the nature and limitation of spontaneous reports, causality has not been established for the following reported adverse events with LIDODERM treatment.

Hypersensitivity reaction, skin irritation, asthenia, paresthesia, hyperesthesia, hypoesthesia, metallic taste, taste alteration, nausea, vomiting, headache, dizziness, lightheadedness, nervousness, somnolence, disorientation, confusion, visual disturbances such as blurred vision, tinnitus, tremor, and flushing.

Systemic (Dose-Related) Reactions

Systemic adverse reactions following appropriate use of LIDODERM are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents, including CNS excitation and/or depression (light headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest). Excitatory CNS reactions may be brief or not occur at all, in which case the first manifestation may be drowsiness merging into unconsciousness. Cardiovascular manifestations may include bradycardia, hypotension and cardiovascular collapse leading to arrest.

OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur. If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS, Systemic Reactions), drug blood concentration should be checked. The management of overdose includes close monitoring, supportive care, and symptomatic treatment. Dialysis is of negligible value in the treatment of acute overdose with lidocaine.

In the absence of massive topical overdose or oral ingestion, evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects, or overdosage from other sources of lidocaine or other local anesthetics.

The oral LD_{50} of lidocaine HCl is 459 (346-773) mg/kg (as the salt) in non-fasted female rats and 214 (159-324) mg/kg (as the salt) in fasted female rats, which are equivalent to roughly 4000 mg and 2000 mg, respectively, in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species.

DOSAGE AND ADMINISTRATION

Apply LIDODERM to intact skin to cover the most painful area. Apply up to three patches, only once for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. Clothing may be worn over the area of application. Smaller areas of treatment are recommended in a debilitated patient, or a patient with impaired elimination.

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides.

When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered.

HANDLING AND DISPOSAL

Hands should be washed after the handling of LIDODERM, and eye contact with LIDODERM should be avoided. The used patch should be immediately disposed of in such a way as to prevent its access by children or pets.

HOW SUPPLIED

LIDODERM (lidocaine patch 5%) is available as the following:

Carton of 30 patches, packaged into individual child-resistant envelopes NDC 63481-687-06

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317

Manufactured by:
Teikoku Seiyaku Co., Ltd.
Sanbonmatsu, Kagawa 769-2695
Japan

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